

ORIGINAL ARTICLE

Injection Anthrax—a New Outbreak in Heroin Users

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SUMMARY

Background: Injection anthrax is a rare disease that affects heroin users and is caused by *Bacillus anthracis*. In 2012, there were four cases in Germany, one of which was fatal, as well as a small number of cases in other European countries, including Denmark, France, and the United Kingdom. Three cases among drug users occurred in Germany in 2009/2010, in the setting of a larger outbreak centered on Scotland, where there were 119 cases.

Case presentation and clinical course: We present three cases of injection anthrax, two of which were treated in Regensburg and one in Berlin. One patient died of multi-organ-system failure on the day of admission to the hospital. The others were treated with antibiotics, one of them also with surgical wound debridement. The laboratory diagnosis of injection anthrax is based on the demonstration of the pathogen, generally by culture and/or by polymerase chain reaction, in material removed directly from the patient's wound. The diagnosis is additionally supported by the detection of specific antibodies.

Conclusion: Injection anthrax may be viewed either as an independent disease entity or as a special type of cutaneous anthrax with massive edema, necrotizing fasciitis in many cases, and about 30% mortality. It has appeared in recent years among heroin users in various European countries. In patients with suggestive clinical presentation and a history of heroin use, anthrax infection must be suspected early, so that the appropriate diagnostic tests can be performed without delay. Timely treatment can be life-saving. It is therefore important that physicians—and the individuals at risk—should be well-informed about this disease.

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Skin infections such as abscesses, erysipelas, and phlegmon are the commonest complications of intravenous drug abuse. The sources of these infections are usually the body's own flora (1). Injection anthrax, however, is probably caused by contaminated heroin and, together with *Clostridium botulinum* and *Bacillus cereus* (*B. cereus*) infections, is one of the rarer causes of severe sepsis following percutaneous application or injection (2, 3). In 2012 so far there have been four cases of injection anthrax in Germany, one of which was fatal. Isolated cases have also been recorded in various other European countries, such as Denmark, France, and the UK. Further cases should be expected. There had already been three cases of injection anthrax associated with drug use in Germany in 2009/2010. That outbreak had centered on Scotland, where there were 119 cases (3). Events have led us to compile this article in order to raise awareness of injection anthrax, among German physicians in particular. To illustrate the procedure to be followed in the event of injection anthrax, the first three cases of anthrax that occurred in 2012 are described.

Etiology

The pathogen that causes anthrax is the Gram-positive, spore-forming, encapsulated bacterium *Bacillus anthracis* (*B. anthracis*), which forms exotoxins (4). Anthrax is a zoonosis that occurs sporadically in Germany in livestock (5), most recently in cows in July 2012 (6). The infection is usually caused by spores, which can survive in their environment for decades, entering the body (7, 8). The vegetative form develops in favorable conditions in the body. This can lead to hemorrhagic disease progression and thereby contamination of the environment via bodily secretions (8, 9).

Approximately 95% of infections in humans are cutaneous (10). Person-to-person transmission is extremely rare. Contaminated heroin is the most likely source of injection anthrax (3). How heroin becomes contaminated is as yet unknown.

Disease progression is essentially determined by the following two virulence factors (11, 14):

- The anthrax exotoxin, which is formed from the protective antigen with the alternatively interacting edema factor and lethal factor
- The bacterial capsule.

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Figure 1 (case 2): Severe erythema with edema of the left breast in a patient infected with anthrax. Perivascular injection in the region of the left clavicle

Among other effects, the toxins trigger immunomodulating and cytolytic processes in the cell (12). Both virulence factors are encoded on plasmids and serve as molecular genetic markers in PCR (polymerase chain reaction) diagnosis of *B. anthracis*. The literature reports isolated cases of *B. cereus* isolates that carry the same or similar virulence factors as *B. anthracis* and can cause comparable symptoms (13–16).

There are four different forms of anthrax, depending on the route of transmission:

- Pulmonary anthrax caused by spore inhalation (e.g. during processing of contaminated animal hides on drums [17] or due to deliberate release of spores using “anthrax letters,” as occurred in the USA in 2001 [18])
- Intestinal anthrax (e.g. from ingestion of meat from infected animals [19])
- Cutaneous anthrax (e.g. from processing animal products from infected animals [20])
- Injection anthrax (probably caused by contaminated heroin [3]).

The mortality rate of intestinal and pulmonary anthrax—when the disease is treated—is approximately 50% (19, 21). For cutaneous anthrax the figure is approximately 5% (10) and for injection anthrax currently around 30% (22). Early initiation of antibiotic treatment is the most important factor in prognosis. Incubation periods range from hours to several days or sometimes even longer (23, 24).

In addition to symptomatic treatment—including surgery for injection anthrax, which is often necessary—antibiotic treatment plays an important role. Various immunoglobulin products, not yet authorized in Germany, that target different toxin components may constitute a complementary approach to the treatment of anthrax (3, 25, 26).

The names of suspected and confirmed anthrax patients and those dying of anthrax are reported to Germany’s Federal Health Office according to Section 6, paragraph 1, point 1, letter j of the German Law on Protection Against Infection (27), as is direct or indirect evidence of *B. anthracis* according to Section 7, paragraph 1, point 2 of the same law (27) if it indicates an acute infection. The Regional Health Office may also initiate independent investigations according to Section 25, paragraph 1 of the law (27) where necessary.

B. anthracis has been classified in risk group 3 (28). Primary diagnosis can be performed using protection level 2 depending on risk assessment, while further diagnostic work based on bacterial cultures requires protection level 3 (29).

Case studies

Case 1:

A heroin user admitted to a hospital in Regensburg on an emergency basis in June 2012 who had consumed various substances on the day of admission. The patient complained of swelling and reddening at an injection site on his/her left upper arm that had been increasing over the last two days, as well as nausea and shortness of breath. He/She had been receiving oral replacement therapy for two years; he/she had many years’ history of heroin, cocaine, and alcohol abuse and was also known to suffer from hepatitis C with cirrhosis of the liver.

The initial working diagnosis was drug intoxication with no pyrexia and significantly compromised general health. Within a few hours the patient was transferred to the ICU due to increasing respiratory insufficiency. Laboratory tests showed leukocytosis, anemia, thrombocytopenia, increased procalcitonin, hypokalemia, and extremely high D-dimer. The patient’s condition deteriorated rapidly and he/she died on the day of admission of septic shock with multiorgan failure and massively disseminated hemorrhaging. *B. anthracis* infection was suspected on the strength of microscopic analysis and MALDI-TOF testing of blood and urine cultures. This suspicion was heightened by initial diagnostic laboratory testing (Microbiology Laboratory, University Hospital Regensburg) the following day using a specific PCR assay, which had been established before as a specific test procedure, and confirmed a day later by further PCR tests at a neighboring expert laboratory (Microbiology Institute of the German Armed Forces [InstMikroBioBw, Institut für Mikrobiologie der Bundeswehr] in Munich) (30).

Case 2:

The individual was admitted to a Regensburg hospital on an emergency basis two days after injecting heroin into his/her left superior thoracic aperture with heroin intoxication and phlegmon of the throat suspected by the treating physician, a specialist in drug users. On admission, the patient’s circulation was stable and intravenous antibiotic (clindamycin, metronidazole,

cefazolin) treatment was initiated. The patient was known to have many years' history of alcohol abuse and hepatitis C.

On the second day after admission cutaneous necrosis and blistering formation occurred, particularly on the lower limbs. This was followed by vivid, clearly delineated, homogenous thoracocervical reddening that covered both mammae, excluding the intertriginous areas and extending to both upper arms, together with swelling and fluctuation, particularly at the left superior thoracic aperture and throat (*Figures 1 and 2*).

Clinical symptoms included general malaise, headaches with no evidence of meningitis, a high fever, and a dry cough. At approximately the same time as the fulminant clinical progression, evidence of *B. anthracis* was found in the blood culture, and treatment with 5 million IU penicillin G4 plus clindamycin and, in particular, 2 × 400 mg ciprofloxacin IV according to infectious disease guidelines, and monitoring in the ICU were begun.

Radiological examination initially showed significant increased streaking in the lungs with no circumscribed infiltrate. Anthrax infection suspected on the basis of medical history and clinical evidence (attention was already heightened as a result of case 1, which had been diagnosed only a few days earlier) was confirmed by the primary diagnostic microbiological laboratory within a few hours using blood culture, MALDI-TOF, and specific PCR assays performed directly on lesion material, as with case 1.

Surgical debridement of the suspected anthrax lesions was performed using jet lavage, and the lesions were dressed using VAC dressings (*Figure 3*). When the lesion on the thigh progressed repeat surgery was performed, three days later.

In addition, the patient developed pneumonia with uneven presentation in the right middle and inferior lobes, with a large pleural effusion. Antibiotic treatment was therefore extended to include carbapenem, and pleural drainage was performed with no microbiological evidence of semination.

On the tenth day after initial surgery it was possible to transfer the patient from the ICU. A total of approximately three weeks' inpatient care was required before the patient could continue to receive treatment on an outpatient basis.

Case 3:

The patient was referred to a hospital in Berlin on an emergency basis in June 2012 by his/her primary care physician. The patient was suffering from suspected deep vein thrombosis following IV injection of heroin into the vein of the right elbow. This patient, too, was known to have multiple drug dependency and chronic hepatitis C.

Four to five days before inpatient admission the patient had noticed progressive swelling, reddening, increased temperature, and pain in the whole right arm, with involvement of the right mamma and upper right chest, and for one day he/she had been suffering from



Figure 2 (case 2): Thigh and popliteal space with severe skin and soft-tissue involvement in anthrax infection. Multiple intravascular and perivascular injection sites in the region



Figure 3 (case 2): Intraoperative findings following excision of necrotic tissue and accompanying jet lavage

fever and shivering. There was also blistering, primarily in the cubital region.

Laboratory tests showed massive increases in infection parameters, including markedly high D-dimer. Following an unsuccessful venography, thrombosis was ruled out using a chest CT. The inflammation was located in the right distal upper arm and the biceps brachii and brachialis with no definite signs of abscess.

Tavanic and clindamycin treatment that had been initiated was switched first to doxycycline after a rash appeared in reaction to medication on the third day, and later to ciprofloxacin monotherapy due to severe recurrent nausea. Local antiseptic measures were then performed using OcteniseptTM dressings, and symptoms improved.

Anthrax infection had been suspected during treatment. This suspicion was first serologically heightened and later confirmed using PCR assays directly on lesion material at a reference laboratory (the Robert Koch Institute, RKI). Testing for the pathogen in the culture 10 days after the beginning of antibiotic treatment was negative.

Figure 4 (case 3): Injection anthrax of the right upper arm following heroin abuse, on referral to dermatology unit

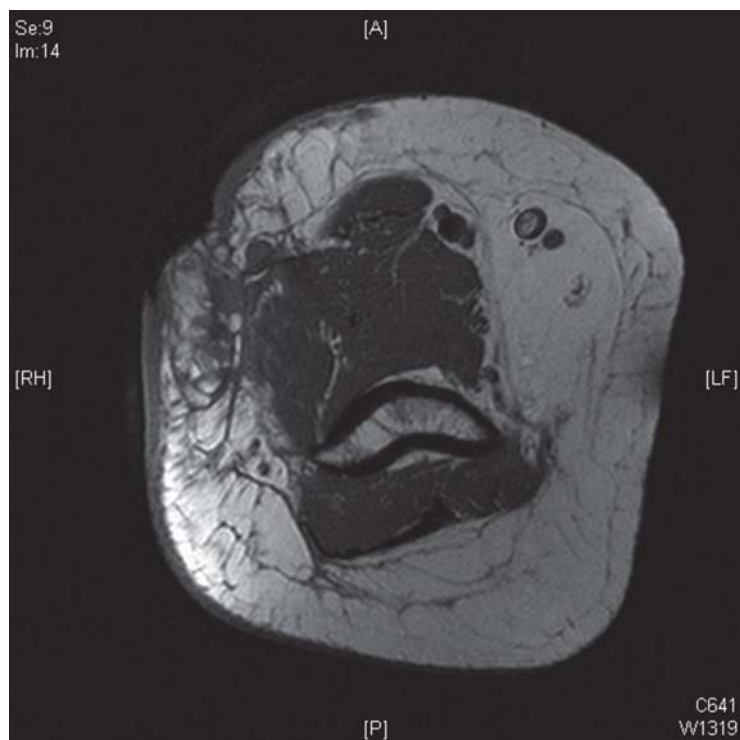


Figure 5 (case 3): MRI of right upper arm before surgical debridement: inflammation of subcutis, no evidence of inflammation spreading to the muscles or bony structures

The patient's clinical progression stagnated and the patient was transferred to a dermatology clinic, where oral antibiotic treatment was extended to include minocycline (Figure 4).

Involvement of deeper layers of skin/fasciae/muscle infiltration was ruled out using MRI, and surgical wound debridement was performed (Figure 5). Continued antibiotic treatment with flucloxacillin and wound treatment using alginate hydrogel led to healing of the lesion. The disease lasted a total of approximately three months (Figure 6).

Laboratory diagnosis

Evidence of *B. anthracis* was found using different methods in each of the three cases.

Evidence from cultures

The blood culture taken from the patient who later died turned positive after only 53 minutes. The blood culture taken from the patient in case 2 turned positive after 3.5 hours. The microscopic presentation of *B. anthracis* was typical. No prior antibiotic treatment had been administered. Isolation of the bacterium was neither possible in the serum sent in for serological testing after the beginning of antibiotic treatment nor in lesion material in cases 2 and 3.

MALDI-TOF MS

The subculture of *B. anthracis* isolates in case 1 was initially identified as *B. cereus* using MALDI-TOF MS (matrix-assisted laser desorption/ionization-time of flight mass spectrometry) (MALDI Biotyper, Bruker Daltonics). Due to the patient's medical history, the received spectra were reanalyzed using another database that also contains safety-relevant organisms (the SR Database). This heightened the suspicion of *B. anthracis* (30).

Serological evidence

In case 3, evidence of antibodies to the *B. anthracis* protective antigen (PA) was initially found in serum using the RKI's accredited in-house testing methods (ELISA, Western blot). From the third blood draw on day 18 onwards, a significant increase in Western blot signal intensity and an increase in ELISA antibody titer from 1:1000 to between 1:2000 and 1:4000 were recorded.

Molecular genetic diagnostics

Within two hours, it was possible to use the positive blood cultures in cases 1 and 2 for real-time PCR-assisted confirmation of diagnosis (30). In addition, evidence of *B. anthracis* DNA was found within four hours in the biopsy material from case 2 and the curettage material from case 3 using various real-time PCR procedures; both patients had already received antibiotic treatment. Interestingly, in case 3 it was possible to isolate *B. anthracis*-specific DNA from lesion material taken repeatedly throughout the observation period of six weeks after initial PCR diagnosis.

Typing

As molecular genetic typing at the Microbiology Institute of the German Armed Forces and the RKI showed, the isolates from cases 1, 2 and 3 (in case 3 only DNA from curettage material was available) were almost identical to each other and to the strain involved in the outbreak described in 2009/2010. In addition, they have characteristic features (31, 32). This may indicate that a single source of infection was involved.

Discussion

Primary clinical differentiation between anthrax and other types of sepsis or phlegmon is impossible. Nevertheless, in cases of life-threatening anthrax early diagnosis is a decisive factor in successful treatment.

Injections in intravenous drug use are frequently followed by inflammatory reactions. Anthrax should be considered as a possible cause of such reactions early in differential diagnosis. In most cases initial microbiological suspicion of diagnosis can be provided by the responsible routine laboratory. To confirm microbiological suspicion or initial findings, or for further description of the pathogen, a reference laboratory such as that of the RKI should be consulted.

In patients who have already received antibiotic treatment, evidence of pathogen DNA using real-time PCR may be possible even several weeks later, as in case 3. In contrast, it is usually no longer possible to isolate living bacteria. If real-time PCR using lesion materials also fails to yield evidence, it is possible to heighten a suspicion of anthrax serologically between one and two weeks or more after infection (the kinetics of antibody formation may vary between patients). In acute cases, it is advisable to take several successive samples for serological testing, in order to observe any titer increase.

In case 2, illness progression was complicated by pneumonia, among other factors. No evidence of the pathogen was found in pleural secretions. Regarding the pathogenesis, in this case the toxic effect of *B. anthracis* should be considered as the primary effect, while bacterial proliferation was brought under control through antibiotic treatment.

B. cereus infection is a possible differential diagnosis. As yet it remains difficult to distinguish between *B. anthracis* and *B. cereus* using MALDI-TOF MS, as there is no free access to appropriate reference databases. Results should always be confirmed by other diagnostic tests with evidence of virulence of markers as well.

Interdisciplinary cooperation is particularly important in cases of rare clinical pictures and little experience treating them. In the cases described here, specialists in infectious diseases, microbiology, ear, nose, and throat, surgery, dermatology, and other areas were involved, and the indication for surgery was reached jointly. Surgical treatment, which should only be provided in conjunction with targeted antibiotic treatment, is extremely important in treating injection anthrax. This clinical picture affects a vulnerable group in which concurrent illnesses are common and compliance with follow-up care can also be a particular challenge.

Staff protection involved measures such as protection of the hands and mouth, and white coats; patients were isolated in the acute stage. Person-to-person transmission is very rare and to our knowledge has never been described in patient care to date. Transmission via wound secretions, however, cannot be completely ruled out. Further information and recommendations on hygiene measures to be taken in the care of anthrax patients can be found on the websites of the RKI and the German Society for Infectious Diseases (DGI, Deutsche Gesellschaft für Infektiologie) (both in German) (33, 34).



Figure 6 (case 3): Presentation of lesion following surgical debridement and switch of antibiotic treatment to flucloxacillin

All three cases, as well as the cases dating from 2009/2010, showed evidence of the same strain of *B. anthracis*. To date, the source of infection, which may be common to all of them, is unknown.

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KEY MESSAGES

- Clinical picture and epidemiological context play an important role in early suspicion of anthrax infection in differential diagnosis.
- In the laboratory, in addition to pathogen isolation from lesion material using real-time polymerase chain reactions, *B. anthracis* can also be detected in the short term, for up to several weeks, after antibiotic treatment. Serological testing may provide further diagnostic evidence, even retrospectively.
- Staff and other patients must be protected using appropriate hygiene measures.
- An interdisciplinary approach to treatment that includes surgical options early on is recommended.
- Future sporadic cases or outbreaks of injection anthrax should be expected.

Conflict of interest statement

The authors declare that no conflict of interest exists.

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